

Identification of Specific Foods Responsible for Inflammation in Children With Eosinophilic Esophagitis Successfully Treated With Empiric Elimination Diet

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See "Management of Children Who Have Eosinophilic Esophagitis" by Putnam on page 129.

ABSTRACT

Objectives: Eosinophilic esophagitis (EoE) is an immune-mediated chronic inflammatory disorder triggered by food antigen(s). A 6-food elimination diet (SFED) excluding cow's milk, soy, wheat, egg, peanuts/tree nuts, and seafood has been shown to induce remission in a majority of children with EoE. The goal of the present study was to identify specific food antigens responsible for eosinophilic esophageal inflammation in children with EoE who had achieved histological remission with the SFED.

Patients and Methods: In this analysis, we retrospectively analyzed children with EoE who completed subsequent single-food reintroductions that led to identification of foods causing disease recurrence. Repeat upper endoscopy with biopsies was performed after single-food introductions. Recurrence of esophageal eosinophilia following a food reintroduction identified that food antigen as a cause of EoE.

Results: A total of 36/46 (25 M/11 F) children who were initially successfully treated with SFED completed this trial; the mean age was 7.6 ± 4.3 years. The most common foods identified were 25 to cow's milk (74%), 8 to wheat (26%), 4 to eggs (17%), 3 to soy (10%), and 1 to peanut (6%). Milk was 8 times more likely to cause EoE compared with wheat, the next most common food (95% confidence interval 2.41–26.62, $P = 0.0007$).

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Conclusions: Serial single-food reintroductions following induction of histological remission with the SFED can lead to the identification of specific causal food antigen(s) in EoE. Cow's milk was the most common food identified in subjects with EoE treated with SFED. A subset of children with EoE may develop tolerance to their food sensitivities while on the SFED.

Key Words: eosinophilic esophagitis, food antigens, treatment

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Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder of the esophagus that is being diagnosed with increased frequency in both children and adults (1,2). Clinical symptoms in children range from food aversion and malnutrition in infants and toddlers, to vomiting in preschoolers and abdominal pain in preteenagers (3). In adolescents, the presentation is similar to adults with symptoms ranging from abdominal pain to solid food dysphagia and food impaction (4). Complications such as strictures have been reported in children and adults (5,6).

The immune-mediated esophageal inflammation is triggered by a food antigen in most children and adults. Subepithelial fibrosis, a precursor to remodeling and strictures that can significantly impair the quality of life in patients with EoE, has been described in children with dysphagia (7,8). The mechanism of subepithelial fibrosis and remodeling is only beginning to be explored, and preliminary data suggest that treatment and reversal of esophageal eosinophilia can result in resolution of the subepithelial fibrosis (9). New evidence in adults who have long-standing EoE shows that persistence of symptoms, despite resolution of acute esophageal inflammation with anti-inflammatory drug therapy, occurs from functional impairment from esophageal remodeling from unchecked prolonged inflammation (10,11). For all of these reasons, identification and elimination of specific food antigen(s) causing mucosal disease offer the best prospect of maintaining sustained histological remission. Thus, reversing unbridled eosinophilic inflammation and accompanying remodeling will prevent functional impairment as well as the likelihood of stricture formation in patients with EoE.

We previously demonstrated that the 6-food elimination diet (SFED) with elimination of cow's milk, soy, wheat, egg, peanut/tree nuts, and seafood resulted in clinical and histological remission in 85% of children (12). A study in adults using the same SFED modality demonstrated histological remission in 50% of study participants (13); however, elimination diets that exclude multiple food proteins from the diet of children in the long term are impractical because they are difficult to implement and can lead to iatrogenic nutritional deficiencies and behavioral problems in recipient children (14–16). Following clinical and histological remission with SFED, the process of orderly, sequential food

reintroduction is initiated; foods are reintroduced at sufficient intervals to document recurrence or continued mucosal healing (17). This process should lead to identification of 1 or more causative food proteins. Excluding only the responsible food(s) from a child's diet can maintain the patient in prolonged remission on a near-normal diet. The goal of the present retrospective study is to report on the subsequent success in identifying specific food antigen(s) causing recurrence of esophageal eosinophilic inflammation in patients who had achieved clinical and significant histological remission with SFED. The secondary goal was to assess whether, in time, patients with specific food protein-induced EoE develop tolerance to the offending food(s).

PATIENTS AND METHODS

Only children and adolescents diagnosed as having EoE and treated with the SFED were included in the study. The criteria for diagnosis and remission of EoE used in our cohort of patients were as previously described (12). Complete remission was defined as ≤ 10 eosinophils per high-power field (eos/hpf) on the SFED. Those who subsequently underwent serial single-food reintroduction leading to identification of specific food antigen(s) causing histologic recurrence characterized by the presence of esophageal eosinophilia were then included. Children who reintroduced a few but not all 6 foods were also included if they demonstrated reactivity to 1 of the reintroduced foods. As in our previous study, eosinophils were counted from an area of the esophagus with the highest number of eosinophils, referred to here as peak eosinophil count. Biopsies were obtained from 2 levels: the distal and the mid-esophagus. Four biopsies from the distal and 4 biopsies from the mid-esophagus for a total of 8 esophageal biopsies as well as gastric and duodenal biopsies were obtained during initial and each subsequent repeat endoscopy.

Study Design and Participants

This observational retrospective study examined a cohort of children with EoE seen at Children's Memorial Hospital (CMH), Northwestern University Feinberg School of Medicine in Chicago, Illinois. Also included were children with EoE examined in a private pediatric gastroenterology practice (S.N.). Between October 2003 and July 2006, 26 children with EoE were successfully treated with SFED excluding cow's milk, soy, wheat, egg, peanut/tree nuts, and seafood proteins from their diet and provided the cohort for the initial publication (12). Since then, an additional 20 children, who demonstrated histological remission when treated with SFED, were also included in the current report. One patient was seen in consultation by 1 of the investigators (A.K.) and the food-reintroduction process was performed under his direction, but all of the endoscopies were performed at a different hospital. Two additional patients who had their initial biopsies done at CMH and completed their food reintroduction elsewhere were studied by 1 of the investigators (T. S.). All of the relevant biopsies for these 3 patients were reviewed by our pathologist (H.M.). All of the patients were maintained on the same proton pump inhibitor dose throughout the period of the food challenge process to differentiate EoE from reflux because both conditions have marked presence of eosinophils. Subjects who achieved histological remission after at least 6 weeks of the initial SFED then sequentially reintroduced the excluded foods generally beginning with soy followed by egg, wheat, and then milk. Peanut/tree nuts and seafood were the last foods introduced. If remission was achieved with a particular food, then that food was retained in the diet and the next food was reintroduced. If there was exacerbation of inflammation with a given food, then it was eliminated from the diet and the next food was reintroduced. Each food reintroduction was followed by endo-

scopy and biopsies done at least 6 weeks from the time the new food was reintroduced as previously described (17). A registered dietitian (S.R.) initially instructed and regularly counseled parent(s)/guardian(s) during the single-food reintroduction process (responding to telephone and e-mail inquiries). Specific written instructions were also given to parent(s)/guardian(s) about how to avoid food cross-contamination by carefully reading labels and, equally important, achieving a balanced age-appropriate diet after eliminating several common foodstuffs. The dietitian also counseled the families throughout the food elimination and reintroduction process, ensuring adequacy of caloric intake and food substitutions to meet all of the protein/caloric needs required for growth. Elemental formula was supplemented in the diet of children whose diet was predominantly milk based to make up for the energy lost by milk elimination.

Outcome Measures

Outcome measures in response to reintroduction of single food proteins were based solely on the esophageal (mid- and distal) peak eosinophil counts in the area of highest density, irrespective of the biopsy examination site. Maintenance of histological remission for the purposes of the present study was defined as a peak eosinophil count of ≤ 10 eos/hpf at least 6 weeks following the food challenge. Partial remission was defined as esophageal eosinophil counts 11 to 15 eos/hpf. Recurrence was defined as esophageal biopsies with > 15 eos/hpf following a specific food reintroduction.

Exclusion Criteria

Patients who were prescribed oral, nasal, airway, or swallowed steroids or the leukotriene antagonist montelukast during the food-reintroduction phase were excluded. Children who did not exhibit histological exacerbation during food reintroductions and who failed to complete a challenge with all 6 foods were also excluded.

Statistical Methods and Analysis

The Wilcoxon signed rank test was used to analyze the differences in pretreatment and posttreatment histology. A generalized linear model with logit link function was used to analyze the association between the allergy status (defined by > 15 eos/hpf) with foods introduced, demographic variables, and clinical variables. Odds ratios and their confidence intervals were estimated to measure the magnitude of association of each food relative to other foods in terms of their risk of causing EoE. A generalized linear model was also applied to investigate the relation between eosinophil counts and foods reintroduced and other clinical variables after considering repeated introductions of different foods to the same subject. The logarithm transformation of eosinophil counts was applied. Significance was defined as a *P* value of less than 0.05. All analysis was conducted with SAS 9.2 (SAS Institute, Cary NC).

Ethics

The study was approved by the institutional review board at CMH.

RESULTS

From our database, we identified 46 (72% boys) children with EoE who achieved histological remission when treated with SFED (Fig. 1). Ten were dropped from the study; 4 did not return after the initial histological remission with SFED for subsequent food reintroductions; 1 patient dropped out before completing the reintroduction of all of the foods and did not react to the foods he

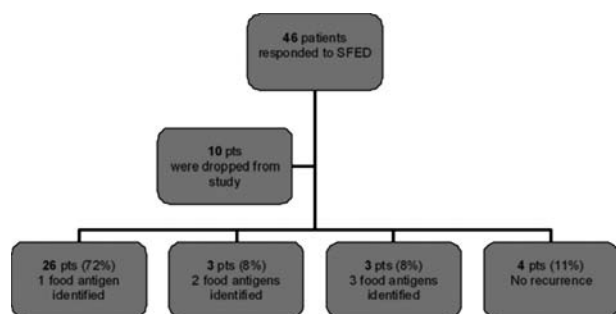


FIGURE 1. Flowchart showing the progression in 46 patients who had achieved remission with SFED. SFED = 6-food elimination diet.

was challenged with until then. One patient was in the process of undergoing reintroduction of foods and had not reacted to any foods reintroduced. Four children with known food allergies could not be rechallenged with the specific food they were allergic to and had not demonstrated disease exacerbation with reintroduction of the remaining foods. Thirty-six patients (25 boys) had mean pre-SFED esophageal eosinophil counts of 93.17 ± 51.75 (median 100.00) and significantly lower ($P < 0.0001$) mean post-SFED eosinophil counts of 3.75 ± 3.92 (median 2.00). The 36 patients either rechallenged with all 6 of the excluded foods or who demonstrated reactivity to 1 or more of the reintroduced foods are described in the present study. The mean age for the group was 7.6 ± 4.3 years. The patient characteristics are shown in Table 1. Single offending food antigens were identified in 26 (72%), 2 foods in 3 patients (8%), and 3 foods in 3 patients (8%) as shown in Fig. 2. Four children completed the 6-food challenge without histologic recurrence. Each of these 4 children were nonatopic. The most common food antigens identified in our patients were cow's milk in 25/34 (74%), wheat in 8/31 (26%), egg in 4/24 (17%), soy in 3/29 (10%), and peanut in 1/17 (6%), as shown in Fig. 3. Cow's milk was the food that most commonly caused EoE. In relation to the other 4 foods, cow's milk was 8 times more likely to cause EoE when compared with wheat, 14 times more likely compared with egg, 24 times more likely compared with soy, and approximately 43 times more likely than peanuts, as shown in Table 2. The likelihood that soy, egg, and peanuts caused EoE was not significantly different from each other ($P > 0.05$). The pretreatment eosinophil count used as the baseline was assumed to be the same as the post-SFED count. The pre- and postchallenge mean esophageal eosinophil counts for each food are shown in Table 3. The esophageal eosinophil counts

TABLE 1. Patient demographics and clinical characteristics (N = 36)

Mean age, y	7.58 ± 4.31
Male sex, n (%)	25 (73.53)
Ethnicity (white/black/Asian/Latino)	30/2/2/2
Atopy (eczema/allergic rhinitis/RAD/food allergies)	8/7/7/10
Presenting symptoms	
Vomiting	15
Dysphagia	15
Abdominal pain	15
Food impaction	7
Malnutrition	7
Anorexia	6
Nausea	6

RAD = reactive airway disease.

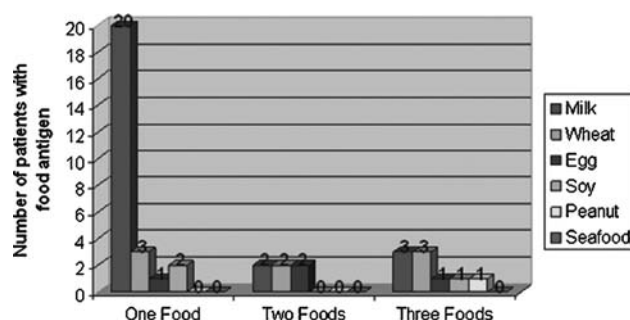


FIGURE 2. Distribution of the patients by the number of food antigens identified. N = 36.

of each individual patient reacting to each food are shown in Fig. 4. Many children did not undergo a rechallenge with seafood and peanuts only because these foods were not part of their initial diet at the time of the diagnosis; for that reason the parents and the gastroenterology team opted not to subject them to the challenge requiring additional esophagogastroduodenoscopies (EGDs). The entire process of reintroducing all of the foods sequentially took place between 5 and 48 months (mean 16.8 months). The mean number of upper endoscopies per patient was 5.6 (range 3–9).

Five patients with follow-up of up to 4 years were rechallenged with food antigens they had reacted to during the initial food reintroduction phase. Repeat endoscopies were done every 1 to 2 years. One of the 3 who was initially allergic to 3 foods including cow's milk, wheat, and peanuts had outgrown her esophageal allergy to wheat and peanuts, but continued to react to milk. Three others who were allergic to cow's milk continued to react when milk was reintroduced for up to 4 years after the diagnosis. One who had not reacted to all 6 foods and who was maintained on a regular diet continued to be in complete histological remission. There were no treatment-related complications and none of the children demonstrated nutrient deficiencies or growth deceleration during the dietary reintroduction phase. There were no procedure-related complications including perforation or bleeding in any of the patients.

DISCUSSION

Our previous study demonstrated that the SFED, excluding cow's-milk protein, soy, wheat, egg, peanut/tree nuts, and seafood, induced resolution in clinical symptoms in most patients and significantly reduced esophageal mucosal inflammation in 74% with EoE and partial histologic remission in an additional 9% of the children (12). We had also demonstrated that SFED, in addition to being an effective treatment modality, is more practical and palatable with the advantage of allowing table food in the diet and was

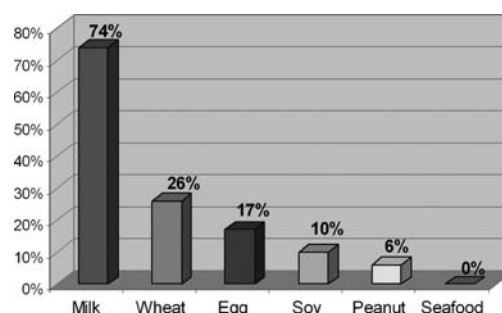


FIGURE 3. Distribution of patients based on individual foods causing recurrence of disease.

TABLE 2. Comparison of food antigens causing EoE

Food comparison	Odds ratio	95% CI	P
Milk vs wheat	8.01	2.41–26.62	0.0007*
Milk vs egg	13.69	3.33–56.25	0.0003*
Milk vs soy	24.35	5.30–111.93	<0.0001*
Milk vs peanuts	42.92	5.71–322.38	0.0003*
Wheat vs egg	1.71	0.54–5.46	0.3654
Wheat vs soy	3.04	0.79–11.70	0.1061
Wheat vs peanuts	5.36	0.85–33.62	0.0733
Egg vs soy	1.78	0.37–8.61	0.4746
Egg vs peanuts	3.13	0.33–29.94	0.3212
Soy vs peanuts	1.76	0.18–17.27	0.6263

The odds of 1 food causing EoE over another. An asterisk indicates the first food is significantly more likely to cause EoE than the latter. CI = confidence interval; EoE = eosinophilic esophagitis.

thus better accepted by patients and their families when compared with an exclusive elemental diet. The present study addresses several limitations of our previous publication on SFED by providing longer-term data about subsequent identification of specific food antigen(s) causing EoE in children who had previously responded to SFED. The present study also provides additional longer-term follow-up in a subset of children who were studied for up to 4 years with EGD surveillance following identification and exclusion of specific food antigens.

Cow's-milk protein was identified in 74% of children as the single most common food antigen causing esophageal eosinophilic inflammation when foods were reintroduced following temporary elimination of 6 foods. After milk, wheat, egg, soy, and peanut were the next 4 most common foods, in that order, causing reactivity in our cohort. Our results are similar to and validated by the results of a comparable prospective study in adults in whom milk, soy, wheat, and egg were identified following progression of the SFED (13). The significance of milk as the most common food antigen causing EoE becomes evident when it is compared with the next 4 foods identified as causing EoE. Milk was 8 times more likely to cause reactivity compared with wheat, 14 times more likely to cause recurrence when compared with egg, and 24 times more likely to cause recurrence when compared with soy. Milk, the most common food antigen, is 43 times more likely to cause EoE than peanut, which is the least common of the 6 foods to cause EoE. In the only other pediatric study in which foods were eliminated based on a combination of skin prick and patch allergy testing, the 4 most common causative foods were milk, egg, soy, and beef. Milk, soy, and egg are identical to our own experience, and unlike in our study, in which wheat was the second most common causative food, a much smaller number of patients in the other study were allergic to wheat (18).

Of the dietary modalities for the treatment of EoE, an elemental diet with amino acid–based formula has demonstrated the highest histologic remission rates in excess of 95% (1). The

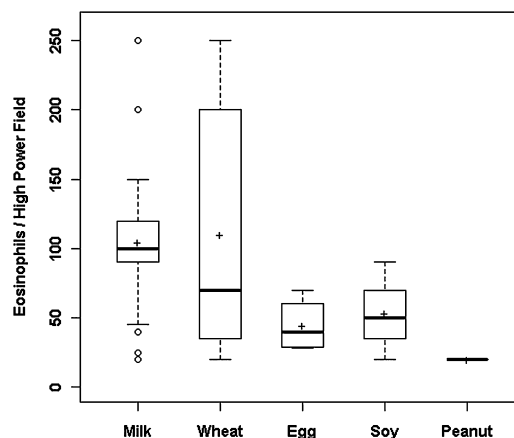


FIGURE 4. Boxplot representation of the distribution of elevated eosinophils in esophageal biopsies to different foods by individual patients. The symbol “+” represents the mean and the horizontal line in the box represents the median eosinophils count.

disadvantages of exclusive elemental diet are manifold: the poor taste of the formula; complete elimination of all food antigens for a protracted period, particularly in small children, can lead to solid food aversion; the subsequent reintroduction process is drawn out over a long period of time with slow introduction of essentially all food antigens; and the high cost of exclusive elemental formula treatment. The only other elimination dietary approach is based on the successful identification of offending food antigens based upon results of skin prick and atopic allergy testing (18). The results of this approach are identical to those of the SFED, but it exposes children to the inconvenience and discomfort of a long battery of skin prick and patch tests. Furthermore, patch testing continues to remain a research tool because of the lack of standardized food antigens, and results from a single-center study await validation (19).

There are several limitations and drawbacks associated with SFED: An important barrier to treatment is that many children still find restricting 6 foods from the diet to be difficult and at times unacceptable, despite its temporary duration and oral route when compared with an elemental diet. This is clearly demonstrated by 5 patients in our cohort who achieved remission with SFED but refused further dietary restriction. Iatrogenic risks of protein energy and micronutrient deficiencies in growing children when 6 major foods, especially milk, are eliminated from the diet even temporarily remain a real concern. It is primarily for this reason that participation of a registered dietitian familiar with food allergies and well versed in food contamination and pediatric nutrition was essential to manage these children and prevent iatrogenic nutritional deficiencies such as kwashiorkor or rickets, which have been described in children treated for food allergies in the United States (14–16,20). One major drawback of the present study is the multiple endoscopies necessary to identify causative food allergens

TABLE 3. Mean eosinophil counts before and after reacting to different foods

	Milk	Wheat	Egg	Soy
Pre- (mean ± SD)	3.04 ± 3.38	2.75 ± 3.69	6.25 ± 2.75	4.67 ± 4.62
Post- (mean ± SD)	105.00 ± 58.51	110.00 ± 92.74	44.50 ± 19.69	53.33 ± 35.12
P	<0.0001*	<0.0001*	<0.0001*	<0.0001*

For statistical purposes it is assumed that the post-SFED eosinophil count is the same as the baseline count before food reintroduction. An asterisk indicates a significant difference between the pre- and posteosinophil counts. SD = standard deviation.

because our study endpoint of response to SFED was established based on histology. This was the single most important reason for a number of patients dropping out of the study before completion of the 6-food challenge. This was also the reason that some parents did not want to have their children subjected to all of the food challenges, especially once an offending food had been identified.

A noninvasive test that would identify recurrence of EoE with a high degree of sensitivity and specificity is not available (21). At the present time there is no validated symptom score index that correlates with histological recurrence after food reintroduction. In the absence of a validated reliable clinical, noninvasive, or minimally invasive biomarker, the only reliable modality to assess disease recurrence is histological assessment of esophageal biopsies. Our patients required a mean of 5.6 endoscopies to correctly identify the triggering food allergen(s). Alternatively, we hope that future studies focusing on understanding the etiopathogenesis of EoE will lead to the identification of novel biomarkers and that in time, these may replace the current need for multiple endoscopies to demonstrate mucosal healing. Another potential drawback of this analysis is that we may have underestimated the total number of foods causing reactivity because many patients did not undergo a challenge with all of the foods, especially peanuts/tree nuts and seafood, if those foods were not in their diet initially. Therefore, it is also possible that some of our patients with single-food elimination may have been allergic to additional foods.

Four of our 36 patients reintroduced all 6 foods without clinical and histological relapse. One of the 4 patients had initially presented with an esophageal stricture. A recent follow-up endoscopy repeated 4 years after her diet was normalized to include all foods again demonstrated normal esophageal mucosa. There are several possible explanations for the normal esophageal histology in these patients. The most plausible is that tolerance to the responsible food antigen has occurred. The other less likely possibilities include induction of the inflammation by environmental inhaled allergens (22). This appears unlikely because the normal endoscopies were performed during the spring and fall, times when patients with environmental allergies are most likely to have histological recurrence. The other possibility is that these 4 patients had gastroesophageal reflux disease and were misdiagnosed and treated for EoE. This is unlikely because by definition, all 4 patients had their diagnostic endoscopies performed after at least 8 weeks of acid suppression with a proton pump inhibitor. Additionally, these children had discontinued acid suppression treatment after the initial diagnostic biopsies. It is also possible that because EoE has a patchy distribution, the normal biopsies could represent a sampling error. We have previously shown that 3 esophageal biopsies have a 95% sensitivity and specificity in demonstrating the presence of inflammation in pediatric EoE (23). We routinely obtain 4 biopsies from the mid- and the distal esophagus for a total of 8 biopsies; therefore, it is unlikely that inflammation, even if it was patchy, could have been missed in these 4 patients. Finally, 1 of these 4 patients underwent repeat endoscopy after being on a normal diet for 4 years and has maintained remission. One of our patients, who was allergic to 3 foods including cow's milk, wheat, and peanut, was rechallenged with the 3 foods after 3 years and has demonstrated tolerance to wheat and peanuts, but continues to react to cow's milk. This patient demonstrates that in time it is possible to develop tolerance to excluded foods.

In conclusion, the present study shows that in a group of children with EoE who had demonstrated mucosal healing with SFED, cow's-milk protein was the single most common food allergen causing esophageal inflammation. The other foods responsible for esophageal inflammation included wheat, eggs, soy, and peanuts. A small subset (<10%) appears to outgrow their initial food-induced EoE. Future large-scale prospective studies addressing elimination of the 4 most common (cow's-milk protein, wheat,

egg, and soy) antigens as well as studies targeting elimination of a single food (eg, cow's-milk protein) are needed to better understand and address the best dietary approach to treating EoE.

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